

**Schizophrenia liability shares common molecular genetic risk factors
with sleep duration and nightmares in childhood**

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Abstract

Background: Sleep abnormalities are common in schizophrenia, often appearing before psychosis onset; however, the mechanisms for this are uncertain. We investigated whether genetic risk for schizophrenia is associated with sleep phenotypes.

Methods: We used data from 6,058 children and 2,302 mothers from the Avon Longitudinal Study of Parents and Children (ALSPAC). We examined associations between a polygenic risk score for schizophrenia and sleep duration in both children and mothers, and nightmares in children, along with genetic covariances between these traits.

Results: Polygenic risk for schizophrenia was associated with increased risk of nightmares (OR=1.07, 95% CI: 1.01 – 1.14, p=0.02) in children, and also with less sleep (β =-44.52, 95% CI: -88.98, -0.07; p=0.05). We observed a similar relationship with sleep duration in mothers, although evidence was much weaker (p=0.38). Finally, we found evidence of genetic covariance between schizophrenia risk and reduced sleep duration in children and mothers, and between schizophrenia risk and nightmares in children.

Conclusions: These molecular genetic results support recent findings from twin analysis that show genetic overlap between sleep disturbances and psychotic-like experiences. They also show, for the first time, a genetic correlation between schizophrenia liability and risk of nightmares in childhood.

Keywords: polygenic risk; genetic correlation; schizophrenia; sleep;
childhood; ALSPAC

1. Introduction

Sleep disturbance is very common in psychotic disorders such as schizophrenia. For example, a meta-analysis of observational studies showed that sleep efficiency and total sleep time are diminished in schizophrenia, whilst sleep latency is increased, independent of medications [1]. These findings are supported by polysomnography studies [2]. Similarly, sleep dysfunction is more common in individuals at ultra-high-risk for psychosis [3], and is associated with higher risk of incident psychotic experiences [4], paranoid thinking [5] and hallucinatory experiences [6] in population-based cohort studies.

A recent report from the Twins Early Development Study (TEDS) demonstrated that psychotic-like experiences and sleep disturbances in adolescence share genetic influences [7]. Using data from 4,800 pairs of twins, they found a mean genetic correlation of 0.54 between self-reported paranoia, hallucinations and cognitive disorganisation, and self-reported sleep quality and insomnia. Bivariate heritability analyses showed that shared genetic influences accounted for on average 65% of the phenotypic correlation between phenotypes. This genetic relationship could be explained in several ways. For example, genetic variants could independently influence sleep and psychotic-like experiences, both sleep and psychotic-like experiences could be affected by a shared genetically influenced process, or there could be a causal relationship between sleep and psychotic-like experiences. We aimed to build on these analyses by using a polygenic risk score derived from the largest genome-wide association study (GWAS) of

schizophrenia to date [8] to investigate the genetic relationship between schizophrenia liability, sleep duration and childhood nightmares through two complimentary approaches.

First, we examined whether genetic risk for schizophrenia is associated with sleep dysfunction during childhood and adulthood in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC). We did this by combining information from the Psychiatric Genomics Consortium (PGC) GWAS into a polygenic risk score that indexes cumulative genetic risk for schizophrenia. The PGC report a variance explained in schizophrenia by the polygenic risk score at a p-value threshold of 0.05 of 7% [8]. This approach has previously shown that genetic risk for schizophrenia is associated with phenotypes such as cognitive deficits [9,10], anxiety and negative symptoms [11] during childhood and adolescence.

Second, we assessed the genetic covariance between schizophrenia and sleep measures in childhood and adulthood using polygenic risk score data to estimate the average genome-wide relationship between these phenotypes.

2. Methods

2.1. Cohort description

ALSPAC is a prospective birth cohort study which initially recruited 14,541 pregnant women living in the Bristol area in the UK, with an expected delivery date from 1st April 1991 to the 31st December 1992 [12]. 14,676 fetuses were included in the initial ALSPAC sample, with 14,062 live births and, of these, 13,988 were alive after 1 year. At 7 years of age further recruitment occurred, resulting in a total sample size for analyses of 15,458, with 14,755 live births and 14,701 alive at 1 year. Data has been collected on mothers and their offspring via questionnaires, clinic visits and other forms of information. The ALSPAC sample is generally representative of the UK population of the same age, although, like many other cohorts, there is over-representation of more affluent groups (6.22% with low household income, as indicated by free school meals, in ALSPAC compared to 12.49% in the National Pupil Database) and under-representation of non-White minority ethnic groups (96.09% White ethnicity in ALSPAC compared to 86.50% in the National Pupil Database) [12]. However, to avoid false positive results from population stratification, our analyses included only those with European ancestry. We also excluded those without both the genetic and the phenotypic data required, leaving between 5,121 and 6,058 children and 2,302 mothers in each analysis. Table 1 summarises the number of individuals with data available for each of the outcome measures. Including all the time points examined for sleep duration, there were a total of 28,138 data points.

Further details of ALSPAC can be found through the searchable data dictionary (<http://www.bristol.ac.uk/alspac/researchers/access/>). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local Research Ethics Committees.

2.2. Phenotypic measures

2.2.1. Sleep duration

Information about sleep duration in children was obtained from parent-completed questionnaire data collected at the ages of 4, 5, 6, 9 and 11 years. Sleep duration was calculated as the difference between reported time that the child went to sleep and time they awoke on weekdays.

Sleep duration in the mothers was assessed through questionnaire data collected when they were on average 40.78 years old (SD=4.52). Participants were asked how many hours and minutes they slept for on work days on average in the last year.

2.2.2. Nightmares

The presence of nightmares was assessed through semi-structured interviews with participants at around the age of 12 and a half years [4,13]. Briefly, children were asked questions about nightmares, night terrors and sleepwalking since their 12th birthday, such as “*Since your 12th birthday have you had any dreams that woke you up? Were they frightening?*”. Positive responses were followed by further questions to distinguish between

nightmares and night terrors. These were then rated as present, suspected or absent. In this study we use data on nightmares only as this was associated with psychotic experiences in a previous study [13] and we wanted to examine whether this extended to genetic risk for schizophrenia.

2.2.3. Covariates

We used the child's sex and age as covariates in the analyses of children's sleep outcomes. We included mother's age as a covariate in the analyses of mother's sleep duration.

2.3. Genetic data

Genetic data for children and mothers was collected in the form of blood samples during clinic visits. Genotyping for children was conducted using the Illumina HumanHap 550quad chip and data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. ALSPAC mothers were genotyped using the Illumina human660W-quad array at Centre National de Génotypage (CNG) and genotypes were called with Illumina GenomeStudio.

Quality control measures were conducted, and SNPs were excluded based on missingness, Hardy-Weinberg equilibrium P value and minor allele frequency. Samples were excluded based on gender mismatches, indeterminate X chromosome, minimal or excessive heterozygosity, disproportionate missingness, insufficient sample replication and evidence of population

stratification. 9,115 children and 500,527 SNPs passed the filters and data was imputed with a phased version of the 1000genomes reference panel from the Impute2 reference data repository. 9,048 mothers and 526,688 SNPs passed the filters and data was imputed using Impute V2.2.2 against the reference panel (all polymorphic SNPs excluding singletons), using all 2186 reference haplotypes (including non-Europeans). After these procedures, removing participants with cryptic relatedness >5% and those who had withdrawn consent, there were 8,252 children and 8,252 mothers with genotype data available.

2.4. Polygenic risk score construction

We constructed polygenic risk scores using Plink version 1.9 [14] for each individual using summary statistics from the PGC schizophrenia GWAS [8]. SNPs with an imputation quality score greater than 0.9 and which were available in ALSPAC were clumped for linkage disequilibrium (LD), using an R^2 of 0.25. We generated weighted polygenic risk scores by summing the number of risk alleles present for each SNP (0,1 or 2) weighted by the logarithm of its discovery sample odds ratio (OR). For estimating covariance (see below) we constructed twelve polygenic risk scores based on different thresholds of the schizophrenia GWAS p-values (0.5 to 1×10^{-7}). The score constructed with a p-value threshold (p_T) of 0.05 captured the most variance in genetic liability for schizophrenia in the PGC sub-datasets [8], so we used this as our primary exposure, with the remainder reported in Supplementary Table 1 and Supplementary Figure 1 in S1 File. Polygenic risk scores were z-standardised, so effect sizes are given per standard deviation (SD) increase

in polygenic risk score. See section 3 of the supplementary methods in S1 File for further details.

2.5. Statistical analysis

2.5.1. Association between polygenic risk score and sleep phenotypes

We conducted statistical analyses in R version 3.2.2 (R Core Team, 2016) and Stata version 14.2 [16]. First, we investigated the association between the polygenic risk score for schizophrenia liability and sleep duration in childhood, by combining all time points into one stacked dataset. We used a linear mixed-effects model, with age nested within family ID as a random effect and covariates age, age² and sex. We tested for an association between the polygenic risk score for schizophrenia liability and nightmares using an ordinal model with sex as a covariate. We tested the association between the polygenic risk score for schizophrenia liability and sleep duration in mothers using a linear model with age as a covariate. To estimate the variance explained by the schizophrenia polygenic risk score at pT 0.05 for each outcome we obtained r-squared values from models without covariates; an adjusted r-squared was obtained from the linear model, a pseudo r-squared was obtained from the ordinal model and a marginal r-squared (the proportion of variance explained by the fixed factors) was obtained for the linear mixed-effects model.

2.5.2 Estimating genetic covariance between schizophrenia liability and sleep phenotypes in childhood and adulthood

Because individual level data were available for the sleep phenotypes and summary data were available for the schizophrenia phenotype, we used the Additive Variance Explained and Number of Genetic Effects Method of Estimation (AVENGEME) [17] to estimate the genetic covariance between schizophrenia liability and sleep duration and schizophrenia liability and nightmares in children, and between schizophrenia liability and sleep duration in mothers. To estimate a genetic model AVENGEME used the T-scores from results of the association between a series of polygenic risk scores at different discovery sample thresholds and the outcomes, sample sizes from the training and test samples, the number of variants used to create the scores, the p-value thresholds used to create the scores and the population prevalence of schizophrenia (we used 0.04) and case/control sampling fractions for the PGC data (0.43). Using this information, the approach is able to estimate the variance explained by genetic effects in the training sample, the variance explained by the polygenic risk score in the outcomes in ALSPAC, the genetic covariance between the training and target samples and the proportion of null SNPs with no effect on the trait in the training sample.

3. Results

3.1 Association between polygenic risk of schizophrenia and sleep phenotypes

3.1.1. Sleep duration in children

We found that a 1SD increase in the schizophrenia polygenic risk score was associated with a decrease in sleep duration of 44.52 seconds (95% CI: -88.98, -0.07; $p=0.05$) (Table 2). This was consistent across other polygenic risk score thresholds (pT 0.01 – 0.5) (Supplementary Table 1 and Supplementary Figure 1 in S1 File). Examining sleep duration at different ages indicates that the effect size increases after age 5 (Supplementary Table 2 in S1 File), although there was little evidence of an interaction between polygenic risk and age when an interaction term was added to the mixed-effects model ($p=0.23$).

3.1.2. Nightmares in children

We found evidence of increased risk of nightmares in those with greater polygenic risk (OR=1.07; 95% CI: 1.01, 1.14; $p=0.02$) (Table 2). We found a similar pattern for other polygenic risk score thresholds (0.05 – 0.5) (Supplementary Table 4 and Supplementary Figure 2 in S1 File). We found no evidence that the proportional odds assumption was violated ($p=0.89$).

Adjusting for the mothers' polygenic risk score in the analyses for sleep duration and nightmares in children had minimal effect (Supplementary

Tables 3 and 5 in S1 File), indicating that the association is not confounded by the mother's psychopathology.

3.1.3. Sleep duration in mothers

The effect size of the association between schizophrenia polygenic risk score and sleep duration in mothers was similar to that seen in children, although evidence in support of this association was extremely weak ($\beta=-57.90$ seconds; 95% CI: -186.57, 70.76; $p=0.38$) (Table 2), most likely because the smaller sample size in the mothers' cohort led to lower power and less precise estimates. The results in mothers for other polygenic risk score thresholds can be seen in Supplementary Table 6 and Supplementary Figure 3 in S1 File, where scores calculated at more stringent p-value thresholds showed small positive associations (0.01 to 1×10^{-7}) compared with small negative associations for pT 0.5 to 0.01.

3.2. Genetic overlap between sleep phenotypes and schizophrenia risk

In the ALSPAC children, our AVENGEME analyses indicate a positive covariance between nightmares and genetic liability for schizophrenia (covariance= 0.07, 95% CI: 0.05, 0.10). We found a negative covariance between sleep duration and genetic liability for schizophrenia in children (covariance= -0.008, 95% CI: -0.20, -0.003) and between sleep duration and genetic liability for schizophrenia in mothers (covariance= -0.04, 95% CI: -0.07, -0.01) (see Supplementary Table 7 in S1 File for full results).

4. Discussion

We investigated whether genetic risk for schizophrenia is associated with sleep outcomes during childhood and adulthood. Our results demonstrate, for the first time with molecular genetic data, that greater polygenic risk for schizophrenia is associated with shorter sleep duration, and we report a new association between greater polygenic risk of schizophrenia and increased risk of nightmares in early life.

These results build on previous twin study findings of shared genetic effects between schizophrenia and disrupted sleep [7] by showing that the association extends to collections of known and measured DNA variants identified through recent well-powered GWAS studies.

The effect size of schizophrenia genetic risk on sleep duration in childhood in this study is small, equating to only a few minutes of sleep difference between individuals scoring three standard deviations above, compared to individuals scoring three standard deviations below the mean for polygenic risk. This is likely to reflect both measurement error in the parent-reported outcome measures, measurement error in the estimation of the effect sizes of the individual DNA variants that make up the polygenic score, and the fact that the pool of variants for the polygenic score is itself an incomplete set of human genomic variation, where many of the variants are imperfect proxies for true causal variants. Because of this, it seems likely that this small effect size is indicative of the stronger polygenic association reported by twin studies. Similarly, although we have reported results for sleep duration, we

have no direct measure of sleep quality, so the marginally lower duration of sleep may index greater disruption in sleep architecture that could have important effects on psychopathology. The R^2 for sleep duration indicates that the schizophrenia polygenic risk score explains 0.02% of the variation in sleep. To put this into context, the PGC article reports that 7% of the variation in schizophrenia is explained by the polygenic risk score [8]. In cross-disorder analyses, the schizophrenia polygenic risk score explains smaller amounts of variation ranging from 0.08% for autism spectrum disorder to 2.3% for bipolar disorder [18], with similarly low variance explained for cognition (<1%) [10]. Therefore, whilst we find a small amount of variation explained in sleep duration, this is on a similar scale to other cross-disorder analyses.

We were, however, able to combine measures of sleep duration from several different ages, which is likely to have reduced error that was not shared across measurement occasions. In addition, the data we used were from a population-based sample that is less likely to be subject to some of the biases associated with ascertainment of clinical samples.

Whilst these findings provide evidence of some underlying shared genetic mechanism between sleep phenotypes and schizophrenia, they do not allow us to determine the reason behind these associations. They could be due to pleiotropy, the phenotypes lying on a causal pathway, population stratification (although this is less likely due to restriction to those with a European ancestry) or a third unknown variable that causes both outcomes, where the PGC schizophrenia GWAS may have an ascertainment bias based on recruitment of those who had experienced this third variable.

Recent studies indicate that there may be a causal relationship. For example, a trial of cognitive-behavioural therapy for insomnia in people with psychosis reported a decrease in persecutory delusions, hallucinations, anxiety and depression [19], suggesting a causal effect of sleep dysfunction on psychopathology post-onset of psychosis. However, another study reported more mixed results with psychosis symptoms [20], and effects of sleep disturbance on incidence of psychosis might differ from those on illness severity. Randomised control trials that examine the impact of sleep interventions on psychosis incidence are not feasible given the incidence rate of psychotic disorders. Our results seem to mostly suggest the direction described in the first study, where disturbed sleep may result in increased risk for schizophrenia as our study finds associations with disturbed sleep in childhood and adolescence prior to any disorder and the association is with schizophrenia risk. However, it is possible that the reverse direction could be true if schizophrenia risk results in sub-clinical symptoms that cause disturbed sleep. There could also be a bi-directional causal association present or no causal association at all. Future well-powered analyses using techniques such as Mendelian Randomisation will be useful for examining whether relationships are causal and the direction of causality.

Conclusion

Our results use molecular data to support and extend the findings from twin studies of an overlap of genetic influences on sleep phenotypes and schizophrenia. We have presented novel findings with our use of polygenic risk scores that specifically relate to liability for schizophrenia risk, as opposed

to psychotic experiences. In addition, we found a novel relationship of shared genetic influences between schizophrenia and nightmares in children.

Data availability

The ALSPAC data management plan

(<http://www.bristol.ac.uk/alspac/researchers/data-access/documents/alspac-data-management-plan.pdf>) describes in detail the policy regarding data sharing, which is through a system of managed open access. The steps below highlight how to apply for access to the data included in this paper and all other ALSPAC data. The datasets used in this analysis are linked to ALSPAC project number B2172; please quote this project number during your application.

1. Please read the ALSPAC access policy (PDF, 627kB) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.
2. You may also find it useful to browse the fully searchable ALSPAC research proposals database, which lists all research projects that have been approved since April 2011.
3. Please submit your research proposal for consideration by the ALSPAC Executive Committee. You will receive a response within 10 working days to advise you whether your proposal has been approved.

If you have any questions about accessing data, please email alspac-data@bristol.ac.uk.

Consent

Written informed consent was obtained from participants or parents of participants, for children. Children were invited to give assent where appropriate. Study members have the right to withdraw their consent for elements of the study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available on the study website (<http://www.bristol.ac.uk/alspac/researchers/research-ethics/>).

Competing interests

No competing interests were disclosed.

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Supplementary Material

Supplementary file 1: Word document containing supplementary tables 1-7 and supplementary figures 1-3

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Table 1. Number of genotyped participants with each outcome measure

Age	Outcome measure	N ¹	Percentage female
<i>Children</i>			
4 years 9 months	Sleep duration	6058	48.6%
5 years 9 months	Sleep duration	5641	48.9%
6 years 9 months	Sleep duration	5534	48.9%
9 years 7 months	Sleep duration	5735	49.4%
11 years 8 months	Sleep duration	5170	50.2%
12 years	Nightmares	5121	51.1%
<i>Mothers</i>			

Average age of 40 years 9 months	Sleep duration	2302	100%
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¹The number of participants with both phenotype and genotype data available

Table 2. Associations between schizophrenia polygenic risk (pT 0.05) and sleep outcomes

Sleep phenotype (units)	Beta or OR	95% CI	R- squared¹	P- value
Sleep duration in children (seconds)	-44.52	-88.98, -0.07	0.0002	0.05
Nightmares in children (ordinal, OR)	1.08	1.01, 1.14	0.001	0.02
Sleep duration in mothers (seconds)	-57.90	-186.59, 70.76	0.00004	0.34

¹The r-squared values were a marginal r-squared (the proportion of variance explained by the fixed effects) for sleep duration in children, Nagelkerke's pseudo r-squared for nightmares and the adjusted r-squared for sleep duration in mothers.

Supplementary Material

Supplementary Table 1. Associations between standardised schizophrenia polygenic risk score and sleep duration in children in ALSPAC.

Risk score p-value threshold	Number of SNPs used	Effect size of association (hours per SD)	95% confidence intervals	P-value
0.5	191,361	-0.014	-0.026, -0.002	0.028
0.4	169,908	-0.013	-0.025, -0.001	0.032
0.3	143,909	-0.013	-0.025, -0.001	0.033
0.2	112,635	-0.014	-0.026, -0.002	0.022
0.1	73,598	-0.013	-0.025, -0.001	0.038

0.05	47,960	-0.012	-0.024, -0.0002	0.048
0.01	18,545	-0.014	-0.026, -0.002	0.022
0.001	5,229	-0.011	-0.023, -0.0008	0.084
0.0001	1,826	-0.005	-0.017, 0.007	0.402
0.00001	737	-0.006	-0.018, 0.006	0.305
0.000001	334	-0.003	-0.01, 0.009	0.644
0.0000001	169	-0.002	-0.014, 0.010	0.745

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 2. Results from linear regressions for sleep duration and polygenic risk score for schizophrenia at each of five time points in childhood in ALSPAC.

	Effect size of association (hours per SD)	95% CI	P-value
4 yrs and 9m	-0.008	-0.026, 0.010	0.365
5 yrs and 9m	-0.008	-0.026, 0.010	0.415
6 yrs and 9m	-0.021	-0.039, -0.003	0.019
9 yrs and 7m	-0.022	-0.040, -0.004	0.012
11 yrs and 8m	-0.016	-0.036, 0.004	0.106

The results shown are for the polygenic risk score constructed at the $p < 0.05$ threshold (47,960 SNPs).

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 3. Associations between standardised schizophrenia polygenic risk score and nightmares in children in ALSPAC.

Risk score p-value threshold	Number of SNPs used	Odds Ratio of association (per SD)¹	95% confidence intervals	P-value
0.5	191,361	1.104	1.037, 1.175	0.002
0.4	169,908	1.102	1.035, 1.173	0.002
0.3	143,909	1.108	1.041, 1.179	0.001
0.2	112,635	1.108	1.041, 1.179	0.001
0.1	73,598	1.098	1.032, 1.169	0.003
0.05	47,960	1.075	1.010, 1.144	0.024
0.01	18,545	1.051	0.988, 1.119	0.117

0.001	5,229	1.025	0.963, 1.092	0.434
0.0001	1,826	1.004	0.942, 1.069	0.910
0.00001	737	0.982	0.922, 1.046	0.577
0.000001	334	1.035	0.971, 1.102	0.290
0.0000001	169	1.008	0.946, 1.074	0.812

¹The odds of the presence of nightmares, compared to suspected nightmares or absence of nightmares

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 4. Associations between standardised schizophrenia polygenic risk score and sleep duration in children in ALSPAC, whilst adjusting for mother's polygenic risk at the same threshold.

Risk score p-value threshold	Number of SNPs used	Effect size of association (hours per SD)	95% CI	P-value
0.5	191,361	-0.012	-0.038, 0.014	0.367
0.4	169,908	-0.011	-0.037, 0.015	0.421
0.3	143,909	-0.011	-0.037, 0.015	0.406
0.2	112,635	-0.013	-0.039, 0.013	0.336
0.1	73,598	-0.021	-0.047, 0.005	0.113
0.05	47,960	-0.018	-0.044, 0.008	0.180
0.01	18,545	-0.022	-0.048, 0.004	0.099

0.001	5,229	-0.015	-0.041, 0.011	0.259
0.0001	1,826	-0.017	-0.043, 0.009	0.205
0.00001	737	-0.011	-0.038, 0.015	0.408
0.000001	334	-0.003	-0.029, 0.023	0.847
0.0000001	169	-0.005	-0.031, 0.021	0.688

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 5. Associations between standardised schizophrenia polygenic risk score and nightmares in children in ALSPAC, whilst adjusting for mother’s schizophrenia polygenic risk score at the same threshold.

Risk score p-value threshold	Number of SNPs used	Odds Ratio of association (per SD)¹	95% confidence intervals	P-value
0.5	191,361	1.072	0.942, 1.220	0.291
0.4	169,908	1.076	0.945, 1.225	0.267
0.3	143,909	1.070	0.940, 1.218	0.304
0.2	112,635	1.078	0.946, 1.229	0.258
0.1	73,598	1.048	0.920, 1.193	0.483
0.05	47,960	1.007	0.885, 1.146	0.912
0.01	18,545	0.993	0.873, 1.131	0.922

0.001	5,229	0.973	0.856, 1.105	0.673
0.0001	1,826	0.925	0.812, 1.054	0.242
0.00001	737	0.900	0.788, 1.028	0.120
0.000001	334	0.969	0.851, 1.103	0.632
0.0000001	169	0.983	0.865, 1.118	0.798

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 6. Associations between schizophrenia polygenic risk score and sleep duration in mothers in ALSPAC.

Risk score p-value threshold	Number of SNPs used	Beta (hours per SD)	95% confidence intervals	P-value
0.5	191,361	-0.029	-0.064, 0.006	0.119
0.4	169,908	-0.027	-0.062, 0.008	0.138
0.3	143,909	-0.022	-0.057, 0.013	0.228
0.2	112,635	-0.021	-0.056, 0.014	0.262
0.1	73,598	-0.015	-0.050, 0.020	0.408
0.05	47,960	-0.016	-0.051, 0.019	0.378
0.01	18,545	0.0001	-0.035, 0.035	0.994

0.001	5,229	0.022	-0.013, 0.057	0.22
0.0001	1,826	0.022	-0.013, 0.057	0.233
0.00001	737	0.022	-0.015, 0.059	0.238
0.000001	334	0.021	-0.016, 0.058	0.271
0.0000001	169	0.009	-0.026, 0.044	0.613

ALSPAC= Avon Longitudinal Study of Parents and Children

Supplementary Table 7. Results from estimating a polygenic model using AVENGEME, with T-scores from the observational associations and the same 12 thresholds used for the polygenic risk score construction.

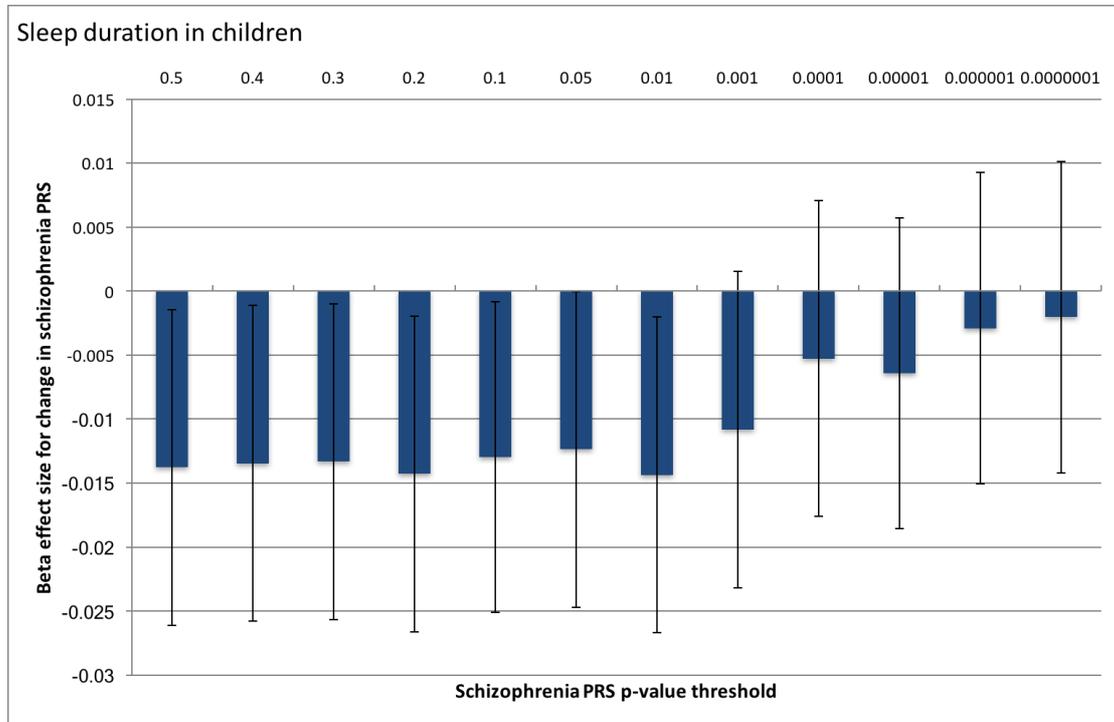
Sleep phenotype	Proportion of trait variance explained (95% CI)¹	Covariance (95% CI)	Proportion of null markers (95% CI)²
Sleep duration in children	0.33 (0.01, 1.00)	-0.008 (-0.20, -0.003)	0.99 (0.92, 1.00)
Nightmares in children (ordinal)	0.28 (0.002, 1.00)	0.07 (0.05, 0.10)	0.51 (0.48, 0.97)
Sleep duration in mothers	0.002 (1.00x10 ⁻⁰⁴ , 1.00)	-0.04 (-0.07, -0.01)	1.43x10 ⁻⁰⁶ (5.46x10 ⁻⁰⁷ , 1.00)

AVENGEME= Additive Variance Explained and Number of Genetic Effects
Method of Estimation, CI= Confidence intervals

¹ The proportion of trait variance explained by genetic effects in the training sample. This is from the regression of the target trait on the polygenic scores

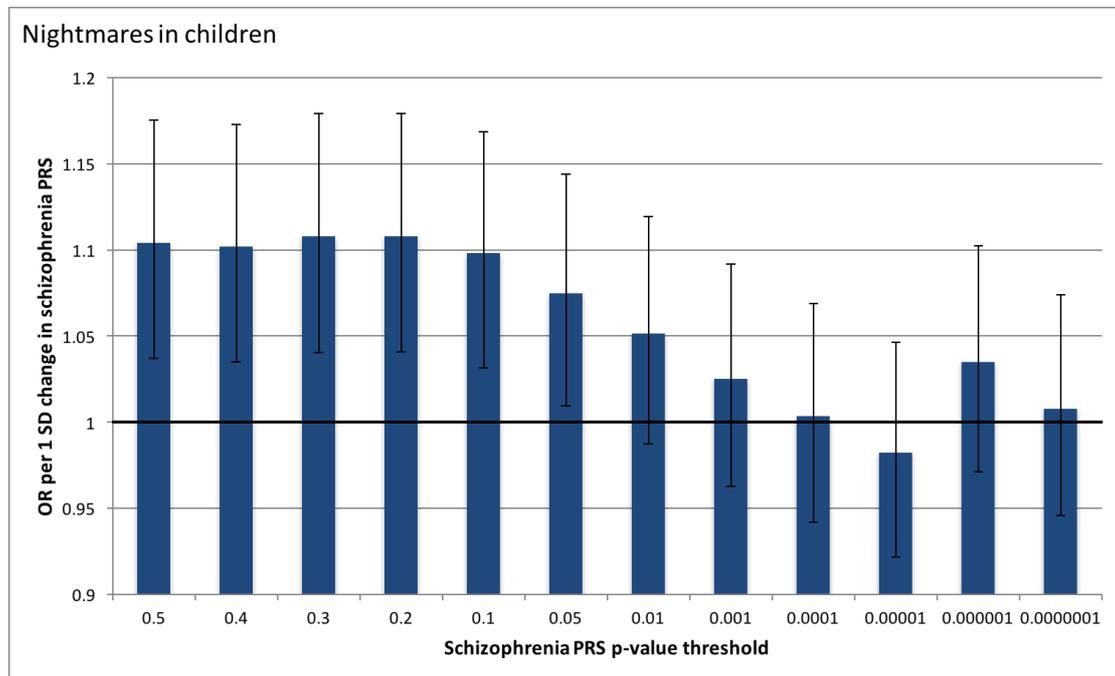
² The proportion of markers/variants with no effect on training trait

Supplementary Figure 1. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and sleep duration in children in ALSPAC.



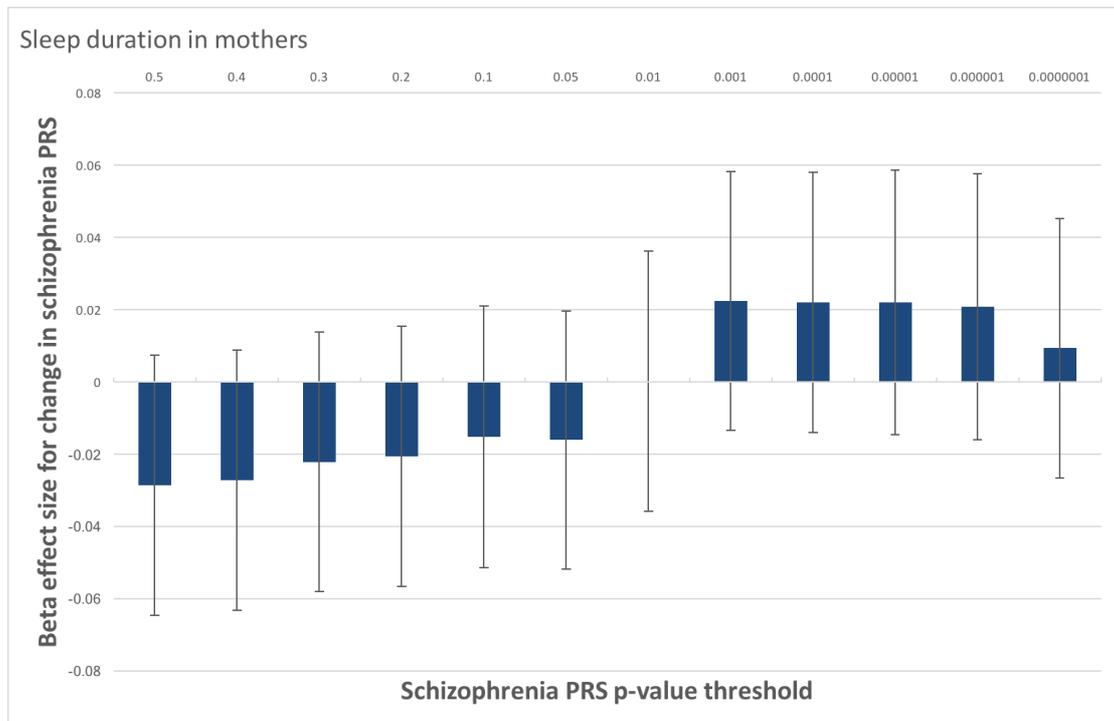
ALSPAC= Avon Longitudinal Study of Parents and Children, PRS= Polygenic Risk Score

Supplementary Figure 2. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and nightmares in children in ALSPAC.



ALSPAC= Avon Longitudinal Study of Parents and Children, PRS= Polygenic Risk Score

Supplementary Figure 3. Associations between polygenic risk score for schizophrenia at 12 different p-value thresholds and sleep duration in mothers in ALSPAC.



ALSPAC= Avon Longitudinal Study of Parents and Children, PRS= Polygenic Risk Score